WHO Stakeholder consultation related to WHA 75.8:

“Strengthening clinical trials to provide high-quality evidence on health interventions

and to improve research quality and coordination”

Pro-forma for FPM response

Question 1

Does the above description capture critical elements of the clinical trials ecosystem? Which elements are missing? Which elements are incorrectly stated? Are you aware of existing up-to-date descriptions of the clinical trials ecosystem relevant to public, private, civil society organisations and philanthropic foundations and all WHO regions? If so, please provide references.

*The resolution requests WHO to lead a consultation process to advance best practices and measures that strengthen the global clinical trials ecosystem. The resolution mentions International Council for Harmonization (ICH) explicitly*

The description provided generally captures the critical elements of the clinical trials ecosystem but does not cite any of the ethical frameworks for the protection of research subjects such as the Declaration of Helsinki and its subsequent amendments – perhaps this is intended under the general heading of ‘governance’.

Question 2

Are you aware of relevant initiatives besides ICH related to strengthening the global, regional, or national clinical trials ecosystems? If so, please fill out the table below with the most appropriate recent initiatives that may be of relevance and should be considered by WHO in actions related to WHA 75.8. Are there adequate clinical trials networks/initiatives covering all WHO regions and all relevant population groups currently, or are they more or less needed? How can capacity development for clinical trials networks in normal times which focus on endemic communicable or noncommunicable diseases best be related to preparations for future pandemics? How best can mechanisms be put in place to trigger a pivot for activity of endemic disease networks towards pandemic response? What is the role of national vs international networks? How can international networks best meet public health needs in each country they operate in?

Many nations have national research systems which promote the conduct of clinical trials: for example here in the UK the National Institute for Health Research, for research in cancer the European Organisation for Research and Treatment of Cancer has been highly influential. Such systems provide possible models for other countries to consider and may be open to forming connected trial networks for international collaborations across multiple individual nation states.

Question 3

WHO’s R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. What additional steps can be taken to facilitate rapid implementation of agreed trial protocols during pandemics and epidemics?

Prospective training and awareness of GCP, trial principles and procedures as part of wider training for frontline health staff in all situations so there is a base level to build on rapidly as needed. Pre agreed research protocols into which relevant diagnostics, treatments or preventive measures (vaccines) might be added on a ‘rolling’ basis. Internationally agreed mechanisms for rapid ethical review and also consideration of health authority review of protocol revisions to enable rapid start up may be helpful – possibly an additional role for ICMRA to consider alongside their work to achieve regulatory alignment on regulatory expectations/amendments to requirements in the face of an urgent medical need.

Question 4

With regard to the resolution text, what do you consider to be “the respective roles of the WHO Secretariat, Member States and non-State actors, [in] … best practices and other measures to strengthen the global clinical trial ecosystem, taking into account relevant initiatives where appropriate”?

*The resolution is related to research waste through its focus on best practices for well-designed and well-implemented trials and its wording on preventing underpowered, poorly designed, or under-reported trials.*

We do not think that this meaning is effectively expressed within the current resolution. There needs to be a much more explicit statement on the poor design and lack of ethical suitability of underpowered studies and the direct harm (to participants) and indirect harm from misleading data or its interpretation, generated as a result (especially in an era of such vast misinformation and disinformation).

Question 5

We define research waste for the purpose of this question to be “any practice that does not allow outcomes of research to contribute to science or public health, including poorly designed, implemented or reported research studies”. What are the best practices in reducing research waste, and what are the roles of WHO, Member States and non-State actors in implementing such best practices?

*The collection, management and sharing of clinical trial data in an ethical and secure manner is fundamental to the conduct and reporting of high quality clinical trials.*

Ensuring there is an agile, consistently used checklist for all who design, review, approve and participate in clinical trials that can ensure minimum standards for studies. One look at the clinicaltrials.gov website shows how this can be put in place to prevent small single centre studies that will not recruit or be interpretable being started. There should be an emphasis on the collaborative nature of research to deliver these aims. The current publications system does not always result in appropriately rapid publication or dissemination of clinical trial outcomes, particularly for studies with negative outcomes, with the result that there may be unnecessary duplication of effort and delay in removing ineffective – worse, potentially unsafe – medicines from study.

Question 6

Many agencies (including WHO) have implemented policies to support data management, sharing and reuse of clinical trials and other research datasets in order to advance science and public health. What measures are needed (legal, technical, other) to ensure that fair and transparent processes are in place to enable access to and reuse of clinical trial datasets in a manner that is appropriate for diverse settings?

Transparency of data and listings as well as clarity on appropriate and inappropriate reanalyses of others’ data to draw different conclusions. Education on integrated and pooled / meta-analyses to understand the balance of evidence and its utility and applicability for guidance and practice. Applicability to different settings and resources (as well as current therapeutic and medical practice) in these settings is essential. Appropriate training on appropriate methods for systematic reviews, including recommendations which may reduce the potential for exclusion of data from such compilations, formal assessment of methods of meta-analysis with recommended ‘best practice’ approaches would be helpful.

Question 7

What do you consider to be measures that can be taken to better utilize digitization and move towards paperless approaches to clinical trials whilst safeguarding subject protections and data quality, measures that are suitable for countries of varying income levels around the world?

Common platforms based on open-source technology with appropriate digital security. Standardised patient record sets facilitate routine collection of data in clinical practice and in turn then results in a higher quality of information being available for ‘draw down’ from healthcare records rather than needing the design of specific reporting instruments when patients are enrolled into clinical studies.

Question 8

What measures can be taken, and by whom, to address the insufficient representation of specific population segments in clinical trials, such as low income countries (LIC) and lower middle income countries (LMIC)populations, pregnant and lactating women, neonates, children, the elderly and the immunocompromised?

Clear statements about the need for and support for research in multiple different locations and settings, as well as an understanding on whether study findings are even applicable to all settings. Caution in interpreting and applying outcomes to wider groups, with a clear rationale as to why some evidence may or may not be applicable. Avoidance of universal applicability without sufficient representation of the data in the setting or patient group in question. Ensure there is a ‘paediatric investigation plan’ (PIP)-like plan for each of these subgroups and settings in the checklist to ensure a plan or programme is in place rather than just an isolated RCT with low relevance. There must be respect for patient autonomy in making a decision concerning trial participation after adequate information is provided concerning the benefits and risks of available treatments and the benefits and risks of participation in a clinical trial when either option is available to them. Facilitating ‘distant’ participation via use of decentralised trial designs may be extremely helpful, particularly for groups of patients for whom travel to a far distant trial centre may not be feasible.

Question 9

What measures can promote clinical trials that address unmet needs in populations that have been neglected or underserved, such as those suffering neglected tropical diseases, rare diseases, the WHO priority list of antibiotic-resistant bacteria and the WHO R&D blueprint priority list.

See above and direct funding to these areas to address the biggest needs.

Question 10

What measures can be taken, and by whom, to ensure evidence generated from clinical trials is considered higher quality from the clinical guidelines perspective, given that ICH already provides guidance for submission of data to regulatory authorities?

*When global research priorities have been agreed, there has been variable success in coordinating funding from research funding agencies to ensure agreed priorities are supported efficiently*

This has to be owned by everyone at all levels. Training and understanding for all HCPs that research is a fundamental driver of care pathways, so data are seen as being a vital element of health decisions and that evidence rather than personal experience drives guidance. Embedding this in the background by training and incentivising all HCPs to be a part of research and seeing their work as research and, whether observational or RCTs, as being of importance in monitoring and adapting practice is key. Results from clinical trials conducted to ICH standards should be rapidly disseminated and the impact of those results on existing clinical guidelines should be considered within a defined timeframe following availability of the data

Question 11

How can research funding agencies work more effectively together, particularly during epidemics and pandemics? And how best can funding address the inequities in current resource allocations to LIC and LMICs? Collaboration and agreement on priorities, and funding these early. Ensuring there are agreed processes that can be put in place to design wider and more applicable studies (like RECOVERY) on an international basis that address the different settings and the use of data in either umbrella design studies or poolable sub studies that prospectively recognise and can adapt for differences in confounders and subsequent guidelines as a result.

*ICH is not explored in question 12, given that ICH has a central role concerning National Regulatory Authority (NRA) submissions of clinical data*

Question 12

Other than ICH, what critical initiatives relate to the resolution and may already have articulated best practices and clinical trials ecosystems, as framed by the resolution? For example, what is your perspective on clinical trials and the CIOMS Working Group report on clinical research in resource-limited settings? What is your view of the Good Clinical Trials Collaborative guidance? WHO International Clinical Trials Registry Platform (ICTRP).

The Good Clinical Trials Collaborative is an example of distillation of the principles of good clinical trial design while the recommendations of the CIOMs working group should, if actioned, strengthen the ability to conduct clinical studies in resource limited settings. Research does need to be appropriate for the context in which it is conducted and it is not the case that a ‘one size fits all’ approach is either necessary or desirable.

Question 13

Given very limited resources, what should be the key priority for improving the ICTRP database, Search Portal and Registry Network to adequately support the clinical trials ecosystem? How can quality of registration data best be improved at both the source registry level and at the ICTRP level to support the aims of the resolution?

The WHO Global Observatory on Health R&D (Observatory) currently provides visualizations of clinical trials globally based on the ICTRP database.

It would be helpful to have a standard data format across all participating registries and perhaps one universal trial numbering system – currently a trial being operated for example in the UK, EU, India, US and Australia will have at least 5 different trial numbers from these systems and yet another for the ICTRP. Might it be possible to work towards one global trial numbering system which is then adopted across all trial registry systems?

Question 14

What measures can be taken to improve visualizations in the observatory?

Question 15

How can the ecosystem lead to efficient adaptation and deployment of capacities during Public Health Emergencies of International Concern (PHEIC)? Please offer examples of best practices and lessons learned. What do you consider best practices of expedited procedures for rapidly implementing clinical trials in PHEIC that meet regulatory and ethics oversight?

Setting up a prospective emergency plan similar to the WHO influenza pandemic plan might be one way to have existing approved programs in place which can be adapted to explore treatments for the condition of concern. The REMAP-CAP program is an example of a ‘ready to go’ protocol approach which could be expanded to additional health regions.

Question 16

If you have any comments, lessons learned, gaps or bottlenecks relating to the clinical trials ecosystem you would like to share, which are not addressed in the previous questions, please provide them here.

Some general comments on the document as follows:

There is not enough emphasis on voluntary participation, data verification and outcome validity or translation to wider practice in prospective design. Neither is there enough on training of those involved in studies. It does not need to be so extensive but there must be sufficient awareness and understanding of trial procedures to make the data reliable consistently.

Line 111 says absolutes are rare - some ‘Musts’ might be helpful - bias, randomisation principles, analyses and power’

Line 125 says uncertainties must be small – that is not always practicable. They must be definable to inform future research requirements and questions

Line 167 et seq refers to sample size. There is a need to consider the inverse relationship between study size and ability to minimise random effects due to wide entry criteria. Wide criteria facilitates wider recruitment but also predicates a need for larger sized studies. These may be more widely applicable but may take longer (so needs to be a factor in timeliness of data), be less well controlled. There is a need to address the balance between size, and variability and quality to offset reliability and interpretability.

Also, there are instances where an intervention is potentially more risky or has known risks whereby a smaller sample size (at least initially) should be used.

Line 224 on outcomes – this should not forget the effect of reliability of measurement, recording and analysis of data as well as sufficient background information to be aware of and potentially interpret the effect of confounding factors. In addition, there should be a sense that an individual study cannot answer the question in all cases, use of meta or pooled / integrated analyses as a prospectively designed programme should be noted.

Line 324 subgroups – these need to be of a sufficient size to be interpretable

Section 5 - Should be clear statement of actual, possible or perceived CoIs and transparency of these and how they may influence the study conduct, design and interpretation. Also, there is no mention of the need to be able to record the data consistently on a CRF or similar consistent platform and to ensure it can be verified to reliable, valid (real pt) and robust

Also, there probably should be a mention of systems to identify systematic errors or uncertainties / Fraud. The question of systems enabling validation of data is not addressed but regrettably fraudulent reports of studies do make their way into the public domain and can cause confusion – the report on efficacy of ivermectin in covid is an example. Hence not only should there be some consideration of trial designs, personnel training etc but also some manner in which trial results can be independently verified.